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阿仑膦酸钠与钙尔奇D分别联合二甲双胍治疗2型糖尿病合并骨质疏松症的疗效对比研究*

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摘要 目的：对比阿仑膦酸钠与钙尔奇D分别联合二甲双胍治疗2型糖尿病(T2DM)合并骨质疏松症的疗效。**方法：**选取我院于2016年4月~2019年1月期间收治的109例T2DM合并骨质疏松症患者，根据乱数表法将患者分为钙尔奇D组(n=54，钙尔奇D)和阿仑膦酸钠组(n=55，阿仑膦酸钠)。比较两组患者临床疗效、血糖指标、骨代谢相关指标、腰椎L2~L4及股骨颈的骨密度值。**结果：**阿仑膦酸钠组治疗1个月后的临床总有效率为83.64%(46/55)，高于钙尔奇D组的62.96%(34/54)(P<0.05)。两组治疗1个月后腰椎L2~L4、股骨颈的骨密度值均升高，且阿仑膦酸钠组高于钙尔奇D组(P<0.05)。两组治疗1个月后骨钙素(BGP)升高，且阿仑膦酸钠组高于钙尔奇D组(P<0.05)；血清Ⅰ型胶原C末端肽(s-CTX)、碱性磷酸酶(BAP)、人抗酒石酸酸性膦酸酶5b(TRAP-5b)则降低，且阿仑膦酸钠组低于钙尔奇D组(P<0.05)。两组治疗1个月后空腹血糖(FPG)、糖化血红蛋白(HbA1c)均降低(P<0.05)，但两组治疗1个月后组间比较无统计学差异(P>0.05)。两组不良反应发生率对比无统计学差异(P>0.05)。**结论：**与钙尔奇D联合二甲双胍治疗比较，阿仑膦酸钠联合二甲双胍治疗T2DM合并骨质疏松症患者，疗效显著，可有效改善骨代谢指标及骨密度，且不影响降糖效果，具有一定的临床应用价值。

关键词：阿仑膦酸钠；钙尔奇D；二甲双胍；2型糖尿病；骨质疏松症；疗效

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A comparative Study of Alendronate Sodium and Calycid D Combined with Metformin in the Treatment of Type 2 Diabetes Mellitus with Osteoporosis*

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ABSTRACT Objective: To compare the therapeutic effects of alendronate sodium and calycid D combined with metformin on type 2 diabetes mellitus (T2DM) with osteoporosis. **Methods:** A total of 109 patients with T2DM with osteoporosis who were admitted to our hospital from April 2016 to January 2019 were selected. According to the random number table, the patients were divided into two groups: calycid group D (n=54, calycid D) and alendronate sodium group (n=55, alendronate sodium). The clinical effect, blood glucose index, bone metabolism index, lumbar L2 ~ L4 and femoral neck bone mineral density of the two groups were compared. **Results:** The total effective rate of alendronate sodium group was 83.64% (46/55), which was higher than 62.96% (34/54) in calycid group D (P<0.05). The bone mineral density of L2-L4 and femoral neck of the two groups increased at 1 month after treatment, and those of alendronate sodium group was higher than that of calycid group D (P<0.05). 1 month after treatment, the level of bone gla protein (BGP) increased in both groups, and that of alendronate sodium group was higher than that of calycid group D (P<0.05). While the level of type I collagen cross-linked C-terminal peptide (s-CTX), bone alkaline phosphatase (BAP), tartrate-resistant acid phosphatase-5b (TRAP-5b) were decreased, and those of alendronate sodium group were lower than those of calycid group D (P<0.05). The fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) of the two groups decreased at 1 month after treatment, and those of alendronate sodium group were lower than those of calycid group D (P<0.05), but there was no difference between the two groups at 1 month after treatment (P>0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). **Conclusion:** Compared with the treatment of calycid D combined with metformin, alendronate sodium combined with metformin has a significant effect on T2DM patients with osteoporosis, which can effectively improve bone metabolism and bone mineral density, and it does not affect the effect of hypoglycemic, which has a certain clinical application value.

Key words: Alendronate sodium; Calcine D; Metformin; Type 2 diabetes mellitus; Osteoporosis; Efficacy

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前言

2 型糖尿病(Type 2 diabetes mellitus,T2DM)是临床常见的内分泌性系统疾病,该病临床多表现为代谢紊乱症群、慢性病变症群以及急性并发症群,若未能及时给予干预,最终将引起患者全身多器官损伤[1,2]。由于 T2DM 患者通常存在着代谢异常,并可引起钙等微量元素代谢障碍而使骨量减少,进而引起骨质疏松症。既往有研究[3,4]指出,糖尿病患者中约有三分之二可出现骨密度下降的现象,而这之中约有三分之一可被确诊为伴有骨质疏松症,给人们的生活造成了严重影响。现临床有关 T2DM 合并骨质疏松症的治疗方案多样,尚未完全统一。钙尔奇 D、阿仑膦酸钠均是临床广泛应用于原发性骨质疏松症的治疗药物,其中钙尔奇 D 可预防和治疗由于钙和维生素 D 缺乏所引起的疾病,而阿仑膦酸钠则是第三代氨基二膦酸盐类骨代谢调节剂[5],可有效抑制人体破骨细胞的活性及骨吸收[6]。现临床有关阿仑膦酸钠与钙尔奇 D 分别联合二甲双胍治疗 T2DM 合并骨质疏松症的临床疗的报道尚不多见,本研究就此展开分析,以期为临床治疗 T2DM 合并骨质疏松症提供参考。

1 资料与方法

1.1 临床资料

选取 2016 年 4 月 ~2019 年 1 月期间我院收治的 T2DM 合并骨质疏松症患者 109 例,本研究已获我院医学伦理委员会批准通过。纳入标准:(1)T2DM 诊断标准参考《中国 2 型糖尿病防治指南(2010 年版)》[7];(2)骨质疏松症诊断标准参考《中国骨质疏松性骨折诊疗指南》[8];(3)经 X 射线确诊为骨质疏松症;(4)均为首次确诊,入组前未接受其他治疗者;(5)患者均按医嘱用药,血糖水平控制一致;(6)患者及其家属知情本研究且签署了同意书。排除标准:(1)近 3 个月使用孕激素、糖皮质激素、降钙素等影响实验结果的药物;(2)对本次研究用药存在禁忌症者;(3)合并心肝肾等功能障碍者;(4)既往有腰椎间盘突出、肿瘤骨转移者;(5)伴有精神意识障碍者;(6)治疗依从性差,中途退出者。根据乱数表法将患者分为钙尔奇 D 组(n=54)和阿仑膦酸钠组(n=55)。其中钙尔奇 D 组男 31 例,女 23 例;年龄 42-71 岁,平均(57.16±7.38)岁;体质量指数(Body mass index,BMI)为 21.6~27.3kg/m^2,平均(24.08±0.96)kg/m^2;糖尿病病程 3-16 年,平均(7.26±1.38)年;平均空腹血糖(Fasting plasma glucose,FPG)(12.48±1.30)mmol/L,平均糖化血红蛋白(Glycosylated hemoglobin,HbA_1c)(9.24±1.13)%。阿仑膦酸钠组男 32 例,女 23 例;年龄 41-70 岁,平均(57.22±6.92)岁;BMI 为 21.8~28.3kg/m^2,平均(24.16±1.03)kg/m^2;糖尿病病程 2-17 年,平均(7.34±1.67)年;平均 FPG(12.41±1.28)mmol/L,平均 HbA_1c(9.20±1.20)%。两组一般资料比较无差异(P>0.05),具有可比性。

1.2 方法

入院后均给予适宜的锻炼、合理的营养膳食及相关疾病健康教育等常规干预。此外所有的患者均给予盐酸二甲双胍片(上海上药信谊药厂有限公司,国药准字 H20123035,规格:0.5 g)治疗,口服,1 g/ 次,2 次 /d,可根据患者具体情况酌情增加剂量。在此基础上,钙尔奇 D 组给予钙尔奇 D(惠氏制药有限公司,国药准字 H10950029,规格:60 片 / 瓶)治疗,600 mg/ 次,1 次 /d。而阿仑膦酸钠组则给予阿仑膦酸钠(Merck Sharp & Dohme S.p.A.,国药准字 J20040004,规格:70 mg)治疗,70 mg/ 次,1 次 / 周。两组均持续治疗 1 个月。

1.3 观察指标

(1)治疗 1 个月后,观察两组患者的临床疗效。疗效判定标准[9]如下:显效:FPG 降低至正常水平,骨密度明显升高,疼痛基本消失;有效:FPG 降低但未恢复至正常水平,骨密度有所改善,疼痛明显减轻;无效:骨密度、血糖以及疼痛症状无改善或加重。总有效率 = 显效率 + 有效率。(2)于治疗前、治疗 1 个月后采用 Prodigy 骨密度仪(美国 GE 公司生产)测定第 L2、L3、L4 腰椎、股骨颈的骨密度值。(3)抽取患者治疗前、治疗 1 个月后的清晨空腹静脉血 6 mL,经 12 cm 的离心半径,3800 r/min 离心 14 min,提取上清液置于冰箱(-20℃)待测。血清中骨钙素(Bone gla protein,BGP)、血清 I 型胶原 C 末端肽(serum type I collagen cross-linked C-terminal peptide,s-CTX)、碱性磷酸酶(Bone alkaline phosphatase,BAP)、人抗酒石酸酸性膦酸酶 5b(Tartrate-resistant acid phosphatase-5b,TRAP-5b)采用双抗体夹心酶联免疫吸附法测定,严格遵守试剂盒(武汉明德生物科技股份有限公司)说明书进行操作。(4)于治疗前、治疗 1 个月后采集两组患者空腹静脉血,采用美国 BECKMAN CX8 型全自动生化分析仪测量 FPG、HbA_1c 水平。(5)记录治疗期间不良反应。

1.4 统计学方法

本研究结果的处理软件为 SPSS21.0,计量资料以($\bar{x}\pm s$)表示,采用 t 检验,计数资料以率表示,采用 x^2 检验,检验水准设置为α=0.05。

2 结果

2.1 两组临床疗效比较

治疗 1 个月后,阿仑膦酸钠组的临床总有效率为 83.64%(46/55),高于钙尔奇 D 组的 62.96%(34/54)(P<0.05);详见表1。

表 1 两组临床疗效比较【例(%)】

Table 1 Comparison of clinical efficacy between the two groups[n(%)]

Groups	Markedly effective	Effective	Invalid	Total effective rate
Calycid group D(n=54)	13(24.07)	21(38.89)	20(37.04)	34(62.96)
Alendronate sodium group(n=55)	18(32.73)	28(50.91)	9(16.36)	46(83.64)
χ^2				5.964
P				0.015

2.2 两组骨密度值比较

两组治疗前腰椎 L2~ L4、股骨颈的骨密度值比较差异无统计学意义（P>0.05）；两组治疗 1 个月后腰椎 L2~ L4、股骨颈的骨密度值均升高，且阿仑膦酸钠组高于钙尔奇 D 组（P<0.05）；详见表 2。

表 2 两组骨密度值比较（$\bar{x}\pm s$，g/cm^2）

Table 2 Comparison of bone mineral density between the two groups（$\bar{x}\pm s$，g/cm^2）

Groups	Lumbar vertebra L2		Lumbar vertebra L3		Lumbar vertebra L4		Femoral neck	
	Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment
Calycid group D(n=54)	0.64±0.07	0.73±0.08*	0.70±0.09	0.78±0.07*	0.69±0.05	0.75±0.08*	0.61±0.06	0.69±0.09*
Alendronate sodium group (n=55)	0.66±0.09	0.79±0.07*	0.72±0.11	0.85±0.09*	0.71±0.08	0.82±2.07*	0.62±0.08	0.77±0.05*
t	1.293	4.169	1.038	4.527	1.562	4.864	0.737	5.750
P	0.199	0.000	0.302	0.000	0.121	0.000	0.463	0.000

Note: compared with before treatment, *P<0.05.

2.3 两组骨代谢相关指标比较

两组治疗前 BGP、s-CTX、BAP、TRAP-5b 比较差异无统计学意义（P>0.05）；两组治疗 1 个月后 BGP 升高，且阿仑膦酸钠组高于钙尔奇 D 组（P<0.05）；s-CTX、BAP、TRAP-5b 则降低，且阿仑膦酸钠组低于钙尔奇 D 组（P<0.05）；详见表 3。

表 3 两组骨代谢相关指标比较（$\bar{x}\pm s$，ng/mL）

Table 3 Comparison of bone metabolism related indexes between the two groups（$\bar{x}\pm s$，ng/mL）

Groups	BGP		s-CTX		BAP		TRAP-5b	
	Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment	Before treatment	1 month after treatment
Calycid group D(n=54)	5.44±0.30	7.08±0.42*	0.57±0.09	0.45±0.07*	31.80±2.10	26.10±3.13*	3.52±0.65	2.78±0.51*
Alendronate sodium group (n=55)	5.43±0.35	9.32±0.45*	0.54±0.08	0.34±0.09*	31.82±3.08	21.33±3.15*	3.56±0.69	2.06±0.45*
t	0.160	26.855	1.840	7.114	0.040	7.929	0.311	7.819
P	0.873	0.000	0.069	0.000	0.969	0.000	0.756	0.000

Note: compared with before treatment, *P<0.05.

2.4 血糖指标水平比较

两组治疗前 FPG、HbA1c 比较差异无统计学意义（P>0.05）；两组治疗 1 个月后 FPG、HbA1c 均降低（P<0.05），但两组治疗 1 个月后组间比较无统计学差异（P>0.05）；详见表 4。

表 4 血糖指标水平比较（$\bar{x}\pm s$）

Table 4 Comparison of blood glucose index levels（$\bar{x}\pm s$）

Groups	FPG(mmol/L)		HbA_1c(%)	
	Before treatment	1 month after treatment	Before treatment	1 month after treatment
Calycid group D(n=54)	12.48±1.30	6.43±0.90*	9.24±1.13	6.88±1.09*
Alendronate sodium group (n=55)	12.41±1.28	6.40±0.83*	9.20±1.20	6.84±1.03*
t	0.283	0.181	0.179	0.197
P	0.778	0.857	0.858	0.844

Note: compared with before treatment, *P<0.05.

2.5 不良反应发生情况

钙尔奇 D 组治疗期间发生 3 例便秘、2 例嗳气，不良反应发生率为 9.26%（5/54）；阿仑膦酸钠组治疗期间发生 2 例恶心呕吐、2 例胃肠道不适，不良反应发生率为 7.27%（4/55）；两组不良反应发生率对比无统计学差异（χ^2=0.142，P=0.706）。

3 讨论

T2DM 合并骨质疏松症是 T2DM 的严重并发症之一，该并发症由多因素作用所致，其具体发病机制主要表现为以下几点：机体长期处于高血糖下，导致患者钙、镁、磷等微量元素浓度下降，同时还可诱导甲状腺功能亢进，促使甲状旁腺激素高表达，导致骨溶增强，患者骨量降低；T2DM 引起的微小血管损伤可影响骨微循环，降低骨新生血管血供；长期的高血糖还可抑制促骨细胞生成，降低骨形成，久而久之发展为骨质疏松症[10-12]。骨质疏松症预防和治疗的关键在于明确骨转化机制以及骨量变化，其中骨转化包括骨形成和骨吸收，故而以抑制骨吸收和促进骨形成是治疗 T2DM 合并骨质疏松症患者的最直接方法[13-15]。钙尔奇 D 是骨代谢调节剂，不仅可促进骨骼骨矿化和钙化，同时还可促进肠内钙、磷的吸收，维持骨钙内环境的稳定，但既往有研究[16]显示钙尔奇 D 长期大量使用易增加结石形成风险。阿仑膦酸钠通过抑制骨吸收，增加骨密度而降低骨折危险，是近年来用于治疗骨质疏松症的热门药物[17,18]，但也有临床实践[19]表明阿仑膦酸钠在恢复已经断裂、变细、甚至消失的骨小梁中的作用较小。

本次研究结果显示，两组治疗后的血糖管理效果基本一致，且两组不良反应发生率对比无统计学差异，安全性较好。二甲双胍作为口服类降糖药物，可通过降低肠道葡萄糖的摄取，进而提高胰岛素的敏感性，有效改善患者血糖状态[20]。同时，阿仑膦酸钠组治疗 1 个月后的临床总有效率高于钙尔奇 D 组，可见相对于钙尔奇 D 联合二甲双胍治疗，阿仑膦酸钠联合二甲双胍治疗 T2DM 合并骨质疏松症患者的疗效更佳。分析其原因，可能是因为钙尔奇 D 对于钙和维生素 D 缺乏所引起的骨质疏松症有较好的治疗效果，但在 T2DM 并发的骨质疏松症，则可能存在一定的疗效不足[21]。而阿仑膦酸钠主要抗骨质疏松症作用机制在于降低骨转换率，抑制破骨细胞活性，恢复骨形成[22,23]。骨代谢标志物是指机体骨转换和骨代谢作用间产生一系列化学物质，主要包括骨形成和骨吸收两大类[24]。其中 s-CTX 的升高可提示人骨质转换效率增强；TRAP-5b 主要存在于破骨细胞内，当破骨细胞活性增强是其水平迅速上升；BGP 主要由成骨细胞合成，可提示机体骨转换情况；BAP 主要分布于人体肝脏、骨骼等组织，在骨质疏松症病人体内发生病理性升高[25-27]。此外，骨质疏松症可发生在患者全身各个部位，其中尤以腰椎、股骨颈等部位发生率最高[28]。本研究中两组患者腰椎、股骨颈处的骨密度以及骨代谢相关指标均有所改善，且阿仑膦酸钠组改善效果更佳，这可能与阿仑膦酸钠进入人体后可特异性结合骨转换活跃的骨细胞上的羟基磷灰石，从而降低机体骨吸收，抑制破骨细胞功能有关[29]，同时阿仑膦酸钠不仅可抑制破骨细胞的功能，还可增加其凋亡速度，降低机体骨丢失速度[30]。

综上所述，相较于钙尔奇 D 联合二甲双胍治疗，阿仑膦酸钠联合二甲双胍治疗 T2DM 合并骨质疏松症患者，疗效显著，可有效改善骨代谢指标及骨密度，且不影响降糖效果，具有一定的临床应用价值。

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